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10/680,287	10/08/2003	G. Roger Askew	032796-179	5825

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HAMA, JOANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/680,287	Applicant(s) ASKEW ET AL.	
	Examiner Joanne Hama, Ph.D.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 09 November 2005.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13,45 and 46 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13,45 and 46 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant has filed a response to the Non-Final Action of June 9, 2005 on November 9, 2005. Claims 1-13 are amended, claims 45 and 46 are new, and claims 14-44 are withdrawn.

Claims 1-13, 45, 46 are under consideration.

IDS

Applicant has filed IDSes on June 16, 2005 and November 7, 2005. These have been considered. The CB reference on the IDS submitted November 7, 2005, Search Report of the European Patent Application EP 92746370, has been considered, but has been lined through because it has no publication date.

Applicant's arguments, see page 13, filed November 9, 2005, with respect to the objection to the IDS (filed January 16, 2004) have been fully considered and are persuasive. The Examiner acknowledges receipt of the Corseaux et al. and Schneider et al. references, which were cited in the January 16, 2004 IDS. The objection to the IDS has been withdrawn.

Withdrawn Rejections

Double Patenting

Claims 1-5, 7-13 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 6-8, 10, 12-15 of copending Application No. 10/477,238 ('238). However, in light of the amendments to the claims of the instant application, the scope of the instant claims are more narrow than that of '238. As such, the double patenting rejection under 35 U.S.C 101 has been withdrawn. It is noted that as the scope of the instant claims has changed, the double patenting rejection for the instant claims has changed from a 101 rejection to an obviousness-type double patenting rejection. See below.

35 U.S.C. § 101

Applicant's arguments, see page 14 of Applicant's response, filed November 9, 2005, with respect to the rejection of claims 1-13 under 35 U.S.C. 101 have been fully considered and are persuasive. Applicant has amended the claims to include the phrase, "non-human". The rejection of claims 1-13 has been withdrawn.

35 U.S.C. § 103

Applicant's arguments, see pages 24-27 of Applicant's response, filed November 9, 2005, with respect to the rejection of claims 1-13 under 35 U.S.C. 103 have been fully considered and are persuasive. Applicant indicates that the teachings of Carulli et al. and Watson et al. do not teach transgenic non-human animals that express HBM in bone. The rejection of claims 1-13 has been withdrawn.

New/Maintained Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13, 45 are newly provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-8, 10-14, 16 of copending Application No. 10/447,238 ('238). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are more narrow in scope than that of the claims in '238. Both inventions are drawn to a transgenic animals; however, the instant claims transgenic animals are "non-human vertebrate" animals, while the '238 are to any animal. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is acknowledged that the Applicant requests that the rejection be held in abeyance until one or more claims are declared to be allowable in the instant or '238 application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 remain rejected in modified form and claims 45, 46 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence, SEQ ID NO. 2, encoding human High Bone Mass (HBM) protein, operably linked to a ubiquitous promoter or a bone-specific promoter, stably integrated in its genome, wherein said mouse exhibits an increase in bone mass in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity,

does not reasonably provide enablement for

a transgenic non-human vertebrate animal comprising a nucleic acid sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at postion 582 of SEQ ID NO. 2 operably linked to any promoter.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, June 9, 2005.

Applicant's arguments filed November 9, 2005 have been fully considered but they are not persuasive.

With respect to the Applicant indicating that the claims as filed do not require transgene expression, let alone any particular level of protein expression (Applicant's response, page 16, 1st parag.), and subsequently, the impact of randomness and copy number of the integrated transgenes on level of expression is irrelevant to the invention claimed in claims 1-3, the Examiner does not find the argument persuasive as follows. The utility of the claimed invention stems from the fact that the transgenic mice comprising the HBM transgene is a model of a human condition, wherein people who have the HBM gene have denser bones. There is no utility for the transgenic mice that comprise the HBM transgene that exhibit no phenotype. As such, the issue that transgene integration and expression levels of transgene is important to practice the claimed invention. While the claims do not indicate a phenotype, the useable transgenic mice are the ones that are the model of a human condition.

It thus follows that with regard to the claims encompassing any transgenic, non-human vertebrate comprising the HBM transgene, merely expressing the transgene in any transgenic animal, other than mouse, does not enable an artisan to practice the claimed invention. While an artisan could take the transgene construct used in the mouse disclosed in the specification and introduce it to other non-human vertebrate animals, the Hammer et al. teachings indicate that transgene constructs do not necessarily have the same biological activities in other species of animals (Office Action, page 16). Again, the utility of the claimed invention is because the transgenic animal exhibits a phenotype like the human condition. Given that the art teaches unpredictability in obtaining other transgenic non-human animal models, an artisan is not enabled for the full, claimed scope.

While the Applicant provides an argument that the claimed invention is enabled for the broad use of any promoter because the specification provides guidance for detecting expression of the transgene (e.g. Northern blot)(Applicant's response, page 18, 2nd parag.), the Examiner does not find the argument persuasive. Again, the reason for this is because the utility of the claimed invention is that it is a model for a human bone condition. Nothing in the art or the specification teaches that HBM has any effect in other tissues other than bone, such that an artisan could readily identify the phenotype associated with HBM expression. In order for an artisan to use a transgenic mouse, wherein the mouse expresses HBM in skin or the nervous system would be undue experimentation because the nothing in the art or specification indicates what characteristics one should look for in the skin or nervous system. As such, an artisan would need to start from scratch to determine whether there is any biological effect of HBM in skin or nervous system.

With regard to the Applicant indicating that the rejection directed to "comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO. 2" is irrelevant because the claims are not directed to transgenic animals expressing or detecting other peptides which may or may not have biological activity (Applicant's response, pages 19-20, point e), the Examiner disagrees. An artisan would need to know the structure-function relationship of the domains in

HBM, in order to obtain a transgenic animal that exhibits a bone phenotype. No utility can be ascribed to an animal that expresses a part of HBM and has no phenotype. With regard to the issue of antisense (Applicant's response, page 20, point f), the claims encompass a nucleotide sequence that comprises at least 15 contiguous nucleotides of SEQ ID NO. 2, including at least the thymine at position 582 of SEQ ID NO. 2. In addition to the sense strand of DNA, which encodes protein, the claims, broadly read, can read on antisense strands. As indicated by Agrawal and Kanimalla (Office Action, pages 17 and 18), making functional antisense strands is not routine and predictable. It is noted that the Office Action indicate that "antisense" was to mean a nucleic acid that reduced the expression level of a target gene (Office Action, page 18, lower part of the 1st parag.), and not a nucleic acid sequence used in RT-PCR or in situ hybridization, as indicated by Applicant to be described on pages 97 and 98 of the specification. Applicant does also indicate the antisense strands on page 105, bottom of the specification, which reduce LRP5 expression in MC3T3 cells. These are the antisense strands relevant to the Agrawal and Kanimala discussion. The Examiner BLASTed the antisense strands (SEQ ID NOs. 639-641) on the NCBI website and found that none of them comprise at least 15 contiguous nucleotides of SEQ ID NO. 2, including at least the thymine at position 582 (NCBI printout of the human LRP5 sequence (NM_002335), Examiner indicates that nucleotide 560 is the same position as nucleotide 582 of SEQ ID NO. 2. BLAST results indicate that none of the nucleotide sequence encompass base 560.). As such, an artisan is not enabled for use of the claimed invention as they encompass antisense strands.

Applicant indicates that the specification discloses a definition of "transgenic" (Applicant's response, page 21, also see specification, page 28), wherein the introduced DNA molecule may be integrated within a chromosome, or it may be extra-chromosomally replicating DNA and as such, should not be limited to the definition provided by the Examiner on page 18 of the Office Action. The Examiner has found the Applicant's argument persuasive and has considered the definition of the claimed invention as it applies to extra-chromosomal DNA. The art teaches that transgenic animals comprising episomal expression vectors can be made (Elbrecht, et al., 1987, Molecular and Cellular Biology, 7: 1276-1279). Elbrecht et al. teach that the transgenic mice in their study were mosaic for the number of copies of transgene vector (Elbrecht, et al., page 1277, 1st col., 2nd parag.). Further, Elbrecht et al. teach that the mice had low copy number of the vector that CAT activity was not detectable (Elbrecht et al., page 1278, 2nd col., 2nd parag.). Elbrecht et al.'s teaching, as it relates to the claimed invention, raises the issue discussed above with regards to expression levels of HBM in the claimed transgenic animals. Elbrecht et al. indicate that the expression levels of a reporter gene are undetectable in their method of generating transgenic mice. This would then indicate that an artisan does not know whether this is a viable method for generating the claimed transgenic animals. Further, in light of the fact that the distribution of the vector in the mouse is mosaic, it is unclear whether enough vector is in bone cells, such that the bone cells can express HBM and cause a bone phenotype. As such, an artisan is not enabled for making transgenic mice using episomal DNA.

The issue of episomal DNA also raises issues that are associated with gene therapy, i.e. an expression vector comprising a gene of interest that is administered to a subject. The art teaches that gene therapy is unpredictable.

The art teaches that there are problems with using vectors to deliver a gene of interest during gene therapy. In the case of a plasmid (non-viral) vector, while they do not raise immune response (Abdallah et al.,1995, Biol. Cell., 85: 1-7, page 1, 2nd col., 3rd parag.), as the viral vectors do, they suffer from inefficient gene transfer (Somia and Verma, 2000, Nature Reviews: Genetics, 1: 91-99, page 91, 1st col., 2nd parag.). The art teaches that using a viral vector as a vehicle to deliver a nucleic acid of interest is unpredictable. These issues of unpredictability include immune responses to the transgene product, the dose of virus administered, the promoter chosen to drive expression of the recombinant gene, the innate immune mechanisms and direct cytotoxcity cause by expression of viral genes (Somia and Verma, page 92, Box 1). In addition to this, while an adenoviral vector remains episomal, and expresses a transgene transiently, some viral vectors, such as retroviral, lentiviral, and adeno-associated viral, will integrate into the genome and express for life-long expression of the transgene (Somia and Verma, page 91, 2nd col., 2nd parag.). However, one major problem with viral vectors that they integrate in the host's genome is that the integration is random. In addition to the problem of random integration being that transcription of the transgene may then become under the control of neighboring factors of the host genome, the problem with random integration is that the transgene may integrate and disrupt a vital gene (Somia and Verma, page 93, 2nd col., 1st parag., see also, page 92, Box 1). As these issues relate to the claimed invention, nothing in the specification provide any guidance that any vector can be used to generate a transgenic animal, such that the transgenic animal exhibits a bone phenotype. As such, because the specification does not provide guidance to overcome the problems associated with viral vectors, an artisan is not enabled for any vectors.

Another problem associated with gene therapy is delivery. The art teaches that,

> "in order for a carrier system to preferentially accumulate at sites of systemic disease, such as tumors, sites of inflammation, and sites of infection, the carrier must exhibit long circulation lifetimes following intravenous injection. Unfortunately, most gene delivery systems including viral vectors as well as non-viral vectors, e.g., lipoplexes, polyplexes, and lipopolyplexes, are rapidly cleared from the circulation and are preferentially taken up by the 'first-pass' organs such as liver, lung, and spleen (Fenske, et al., 2001, Current Opinion in Molecular Therapeutics, 3: 153-158, see abstract)."

As this situation applies to the instant invention, nothing in the specification provides guidance as to how to administer a vector comprising a nucleic acid sequence encoding HBM, such that the vector arrives at the bone cells, expresses HBM, and effects a bone phenotype. It is noted that the vector has to arrive at bone cells because HBM is a receptor and is not a diffusible protein. As such, the specification does not provide guidance for an artisan to practice the claimed invention for an episomal vector.

The amended claims read on a transgenic animal comprising a human bone cell transplant. At the time of filing, the art teaches that cell and organ transplantation is unpredictable. With regards to a xenogeneic or allogeneic transplant, one major problem associated with these transplants is loss or rejection of the cell. The loss or rejection stems from an immune response to the foreign cell (Platt, 1998, Nature, 392 supplement: 11-17; page 11, 2nd col. under "The barriers to xenotransplantation". While one might use drugs to immunosuppress a host, the specification does not teach what those drugs may be nor does the specification teach how to administer such drugs (which drugs, how much, route of delivery, for what duration of time). In addition to this, a skilled artisan would need to know how to prevent infection of the host organism, while the host's immune system is suppressed (Platt, page 14, Box 1, 1st parag.). One may suggest that syngeneic cells could be used to circumvent the problem with cell rejection. Certainly, this is a possibility as Gage teaches that syngeneic cells need not integrate into a homotypic region (Gage, 1998, Nature, 392 supplement, pages 18-24; page 18, 2nd col., 1st parag. under "Function of cells as implants"). However, if long-term survival is required, success of the graft appears to depend on the cell type, the site of implantation, and type or class of promoter (Gage, page 19, 1st col., lines 2-5). Alternatively, if in the cases that require a cell to integrate into a homotypic region and perform specific physiological roles, a skilled artisan would need to know the phenotype of the cell and the spatial location critical to its utility (e.g. a retinal cell transplant or a skin graft) (Gage, page 19, 1st col., 2nd parag. to 2nd col., 2nd parag.). In addition to selecting a cell, a skilled artisan would need to consider that the transplanted cell would be comprised of a DNA expression vector. The art teaches that sometimes following transplantation, a cell comprised of a transgene may alter its level of transgene expression. For example, Fisher teaches that a neuronal cell line, RN33B, show loss of β-gal labeling in cells grafted in the CNS. The change in gene expression does not appear to be because the skilled artisan used a retrovirus. Gene expression is also compromised in cells wherein adenovirus or herpes virus vectors were used (Fisher, 1997, Neurobiology of Disease, 4: 1-22; page 15, 2nd col., 2nd parag. under "In vivo considerations of genetically modified cells," lines 1-13). Thus, for reasons described above, a xenogenic or allogeneic transplant of faces the problem of host rejection. The methods involved to reduce the chance of rejection would need to be empirically determined. Coupled with this, to reduce rejection may involve methods of reducing infection in the host. This, too, would need to be empirically determined. In the case of syngeneic cells, a skilled artisan would need to be taught what kind of cells would need to be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined. Finally, whether a transgene construct can be reliably expressed would also need to be considered. Thus, for the reasons described above with regard to cell transplantation, the specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

As such, claims 1-13, 45, 46 are not enabled for their fullest breadth.

Claims 1-13, 45, 46 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record, June 9, 2005.

Applicant's arguments filed September 9, 2005 have been fully considered but they are not persuasive.

While Applicant provides an argument indicating that the specification provides written description guidance on pages 22-24 of Applicant's response, the Examiner does not find the argument persuasive. The point that the Examiner was making in the written description section was that the claims broadly encompass a variety of nucleic acid sequences, wherein the nucleic acid sequences are at least 15 contiguous nucleotides of SEQ ID NO.2, including at least the thymine at position 582 of SEQ ID NO. 2. The first issue this raises is: what biological activities do these peptides have? Nothing in the specification provides guidance that a certain domain of the protein, or a certain structure of the protein has a specific biological function, such that when it is in the bone cell, it has a biological effect. It is noted that the specification provides some guidance as to structure of LRP5 (it is has 4 beta-propeller structures, specification, page 47). However, nothing in the specification provides guidance what biological function(s) these structures have. The second issue that is raised is that the claims are broadly encompass peptides encoded from the nucleic acid sequence of SEQ ID NO. 2, wherein the peptides are generated from any reading frame. No guidance was given as to what structures these peptides have and what biological activity they have. The third issue is that the claims also encompass antisense nucleic acids. Nothing in the specification provide guidance as to what structures these antisense nucleic acids have, such that they bind to nucleic acids that encode LRP5 or HMB and inhibit protein expression.

While the specification provides guidance for an artisan to obtain the claimed transgenic mouse, wherein the transgenic mouse expresses SEQ ID NO. 2 in bone and exhibits a bone phenotype, the specification does not provide guidance for the breadth of portions or parts of SEQ ID NO. 2, such that an artisan can obtain a transgenic animal comprising a phenotype associated with a human disease or condition.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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